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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/393,795	09/10/99	GRAY J	CMCC693P2A

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EXAMINER	
LEFFERS JR,G	
ART UNIT	**PAPER NUMBER**
1636	15

DATE MAILED: 12/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/393,795	Applicant(s) Gray, et al.
	Examiner Gerald G. Leffers Jr.	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Sep 29, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-49* is/are pending in the application.

Of the above, claim(s) *4, 6, 11, 15, 19, 21, 26, 30, 34, and 38-49* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33, and 35-37* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *10 and 13*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Receipt is acknowledged of applicants' amendments filed 8/18/00 (Paper No. 12) and 9/29/00 (Paper No. 14). Also, supplemental Information Disclosure Statements (filed 5/09/00 and 9/7/00) have been received and the cited references have been considered. The corresponding PTO 1449 forms have been signed and initialed, and have been mailed along with the instant Action. Claims 1-49 are pending.

Applicant's election of Group I (claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37) in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 4, 6, 11, 15, 19, 21, 26, 30, 34 and 38-49 are withdrawn from consideration as being drawn to a nonelected invention.

The claims have been amended to specify that the packaging cell lines, methods of constructing and using such cell lines and the particles produced by such cell lines, feature the use of a retroviral nucleotide sequence (i.e. packaging vector) which comprises a codon-optimized HIV or lentiviral gagpol sequence but not coding sequences for HIV or lentiviral accessory proteins or constitutive transport elements. In response to this amendment, the rejection of all claims remaining under consideration has been made under 35 U.S.C. 112, first paragraph. Accordingly, this Action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for packaging cell lines (as well as methods of constructing/using such cell lines or the particles produced from such methods) featuring a first lentiviral nucleotide sequence which comprises codon optimized coding sequences for gagpol operatively linked to a Rev Response Element (RRE) and which does not also comprise coding sequences for the viral accessory proteins or a constitutive transport element (CTE), does not reasonably provide enablement for embodiments wherein the first lentiviral nucleotide sequence does not comprise the gagpol sequences operatively linked to a RRE. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. **This is a new rejection necessitated by applicants' amendments filed 8/18/00 and 9/29/00.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the art, state of the prior art and the amount of

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The nature of the claimed invention is extremely complex, encompassing the combination of optimizing expression of lentiviral structural genes by optimization of nucleic acid coding sequences for the structural gene (i.e. codon optimization) with an absolutely minimal viral packaging system wherein coding sequences for lentiviral accessory proteins have been eliminated from the packaging vector as well as cis acting elements required for nuclear-cytoplasmic transport of RNAs encoding the lentiviral structural proteins. Applicants propose that such a system would result in increased expression of gagpol structural genes and thus an increase in viral titre and result in less frequency of recombination to produce wildtype or infectious virus while producing viral particles which do not comprise lentiviral accessory proteins.

Breadth of the claims: The complexity of the invention is exacerbated by the limitation in each of the claims that the packaging vector which comprises and expresses the codon optimized gagpol sequence lacks the coding sequences for any of the lentiviral accessory proteins (e.g. Tat, Vif, Vpr, Vpu, Nef and Rev) as well as any constitutive transport elements (CTEs). This very specific limitation means, in at least some embodiments, that the vector system/packaging cell line must be able to express the gagpol sequences and transport the gagpol message to the cytoplasm from the nucleus in the packaging cells of the system without the

Rev/RRE system or some compensating constitutive transport element operatively linked to the gagpol message.

Guidance of the Specification: All of the teachings provided by the specification regarding such a packaging system wherein the packaging vector does not comprise coding sequences for any of the accessory proteins and does not also possess a CTE element operatively linked to the gagpol sequence are merely prophetic in nature. The specification merely states that such a vector system is possible without providing guidance as to how the gagpol sequences expressed from the packaging vector are capable of transport from the nucleus to the cytoplasm in the absence of a Rev/RRE or CTE component. No guidance is provided as to how one would make such a system work in the event that the plasmid system described in the specification (e.g. pages 12-13, bridging paragraph) does not work to produce packaged viral particles as predicted. The specification does not describe such a system wherein the packaging vector lacks the coding sequences for the accessory proteins, has a Rev response element (RRE) operatively linked to the gagpol sequence and Rev is supplied in trans from another source.

The Existence of Working Examples: The specification provides no working examples nor any indication that a system wherein the lentiviral packaging vector lacks a RRE or CTE component operatively linked to the gagpol coding sequences actually produces recombinant lentiviral particles lacking accessory proteins.

The State of the Art: The state of the art for developing lentiviral packaging systems wherein most or all of the accessory proteins have been deleted is relatively high. The state of

the art for such a lentiviral packaging system wherein the packaging vector which lacks the coding sequences for the accessory proteins does not also have a means for transport of expressed gagpol message from the cytoplasm to the nucleus (e.g. RRE/Rev or CTE) is not high. An operative system featuring the limitations recited by the rejected claims and which does not also have a RRE operatively linked to the gagpol sequence does not appear to have been described in the prior art. In fact, the prior art teaches that the presence of some sort of transport element, either a Rev/RRE element or CTE, operatively linked to the gagpol coding sequences is essential for formation of recombinant viral particles in a minimal lentiviral system wherein most of the accessory proteins have been omitted. For example, Kim et al (AT; Journal of Virology, Vol. 72, No. 1, pages 811-816; see entire document) teach a minimal HIV vector system in which the packaging vector expressing the gagpol sequence either possesses an RRE or CTE operatively linked to the gagpol sequence (Figure 1; Table 2; page 812, paragraph 4 to page 813, paragraph 2). Kim et al teach that their minimal system lacks tat, vif, vpr, vpu and nef and requires only the rev/RRE accessory system, or alternatively a MPMV CTE component in its place (page 814, paragraph 3). Kim et al demonstrate that their minimal system, analogous to that claimed by applicants, does not function to produce viral particles in the absence of cis-acting transport elements operatively linked to gagpol (Table 2).

Predictability of the Art: Given the teachings of the prior art that a minimal system analogous to that claimed by applicants requires the presence of either a CTE operatively linked to the gagpol sequence, or a RRE component operatively linked to gagpol with Rev supplied in

trans, the success of the system claimed by applicants lacking such components operatively linked to gagpol is not at all predictable.

The Amount of Experimentation Necessary: Given the complexity of the invention which is compounded by the limitation of a lentiviral packaging vector lacking coding sequences for any of the viral accessory proteins (specifically for Rev) and which also does not comprise a constitutive transport element for the gagpol sequence, the apparent novelty of such a system in the prior art, the lack of working examples of such a system in the specification, the teaching of the prior art that such a minimal lentiviral packaging system requires either Rev/RRE elements or a CTE element and the lack of guidance in the specification for how such a system lacking any evident means for transport of the gagpol message from the nucleus to the cytoplasm of the packaging cell would actually produce enough gagpol to package recombinant lentiviral particles, it would require undue, unpredictable experimentation to make and use applicants' invention. Therefore, applicants invention of packaging cell lines, methods of constructing/using such cell lines and the lentiviral particles produced from such cell lines, wherein the packaging vector expresses an optimized gagpol sequence yet does not express coding sequences of any accessory proteins and which does not comprise a cis-acting transport element (e.g. CTE or RRE) operatively linked to gagpol, is not considered to be fully enabled by the instant specification.

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to specify that the packaging cell lines, methods of constructing and using such cell lines and the particles produced by such cell lines, feature the use of a retroviral nucleotide sequence (i.e. packaging vector) which comprises a codon-optimized HIV or lentiviral gagpol sequence but not coding sequences for HIV or lentiviral accessory proteins or constitutive transport elements. There is no support in the specification for the specific limitation of a first nucleotide sequence which comprises a codon-optimized gagpol sequence and, yet, does not comprise coding sequences for any accessory protein or for a constitutive transport element. The closest support for such a packaging vector is the vector described on pages 12-13, bridging paragraph, wherein the first nucleotide sequence expressing a codon-optimized gagpol sequence does not comprise any of the coding sequences for the lentiviral accessory proteins, does not comprise a constitutive transport element (CTE) and further does not comprise a Rev Response Element (RRE). As noted above, there is an important functional distinction between the vector claimed and the one described in the specification. The claimed vector allows for Rev-dependent transport of the gagpol message from the nucleus to the cytoplasm of a packaging cell, whereas the described vector does not. Therefore, the cited new limitation constitutes NEW MATTER and should be dropped from the claim language.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GJL

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER

December 10, 2000